Remarks

I. Summary of Claim Amendments and Amendments to the Specification

Claims 1-3, 8, 20, 21, 25, 30, 35, 55, 59, 60, 69, 89, 90, 94, 108, 112, 125, 138, 158, 176, 177, 179, 180, 181, 184-186, 190-192 have been amended to indicate that aliphatic groups and heteroaliphatic groups are non-aromatic. Support for this amendment can be found on page 11, lines 1-24 and page 13, line 34 to page 14, line 2 of the specification which lists numerous illustrative examples of aliphatic groups and heteroaliphatic groups, none of which is aromatic.

Applicants have amended Claim 1 such that R_A is not an aliphatic or heteroaliphatic group substituted with one or two phosphorus containing moieties. Support for this amendment can be found in the specifica examples listed on page 90-108 of the specification which shows no examples in which R_A is an aliphatic or heteroaliphatic group substituted with two phosphorus containing moieties.

Applicants have amended the definition of R_B in Claim 1 to replace heteroaliphatic with heterocycle. Support for this amendment can be found on page 13, line 36 to page 14, line 6 which indicates that heterocycle groups are a subgenus of heteroaliphatic groups. Note that Applicants use the terms "heterocycle" and "heterocycloalkyl" interchangeably (see page 14, lines 25-32 of the specification).

Applicants have amended Claim 1 to incorporate the limitation of Claim 9 that R_D is hydrogen and removed the proviso regarding R_D since it is no longer applicable. In addition, Applicants have cancelled Claims 9, 11, 12, 29, 63, 99 and 117 because they are redundant in view of the amendment to R_D. Applicants have also amended Claims 3, 7, 8, and 15-17 to make the claim language consistent with Claim 1.

Applicants have amended Claims 2, 3, 125, 158, 177, 180, 181, and 186 such that X in the group $-P(X)YR_GYR_H$ can be absent, =O or =S instead of an alkyl group, =O or =S. Support for this amendment can be seen in the structural formulas of compounds of the invention shown on page 106 of the specification. The structural formulas show phosphorus containing groups having the formulas $-P(O)YR_GYR_H$, $-P(S)YR_GYR_H$, and $-PYR_GYR_H$. Applicants have also amended the specification such that the definition of X corresponds with this claim amendment. No new matter has been added since the amendment is supported by the structural formulas on page 106 of the specification.

Applicants have amended Claims 2, 20, 55, 89, 108, 125, 158, 177, 180, 181, 185, 186, 191, and 192 and the specification to correct an obvious error in the valency of M in the phosphorus containing moiety. A person of ordinary skill in the art would immediately realize the obvious error in the valency and be able to discern the structure inserted herein by amendment. Therefore, the amendment does not constitute new matter.

Applicants have amended Claims 2, 3, 8, 20, 21, 25, 55, 59, 89, 90, 94, 108, 112, 125, 158, 177, 179, 180, 181, 185, 186, 191, and 192 to replace $-N(R_J)_2$ with $-NR_J-$ as a choice of substituent for Y. Support for this amendment can be found in the definition of the term "phosphorus containing moiety" on page 15, lines 19-21 of the specification which indicates that a phosphorus containing moiety can be a phosphonic acid amide.

Applicants have amended Claims 7, 8, 21, 26, 60, 90, 96, 114, 129, 178 and 179 to replace the terms "acylamino" and "amido" with $-CONH_2$, -CONH-alkyl, -CONH-aryl, -CONH-heteroaryl, -NHC(O)-alkyl, -NHC(O)-aryl, -NHC(O)-heteroaryl as substituents for R_A, R_B, R_C and R_2. Applicants have replaced "aldehyde" with the chemical formula for an aldehyde substituent (i.e., -C(O)H), and Applicants have replaced the term ketone with -C(O)-alkyl, -C(O)-aryl, and -C(O)-heteroaryl. Support for these amendments can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

Applicants have amended Claims 7, 8, 21, 26, 60, 90, 96, 114, 129, 178 and 179 to replace the term "sulfonyl" with $-SO_2$-alkyl and $-SO_2$-aryl. Support for this amendment can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

Applicants have amended Claims 8, 21, 26, 90, 129, and 179 to delete carbonyl and thiocarbonyl from the list of optional substituents for an aromatic ring.

Applicants have amended Claims 31-33, 65-67 and 134-136 to replace the term "acyloxy" with -OC(O)-alkyl, -OC(O)-aryl, and -OC(O)-heteroaryl. Support for this amendment can be found on page page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

Applicants have corrected a typographical error in Claims 18, 53, 87, 104, 122, 157, and 172 by amending the phrase "one of more" to read "one or more."

Applicants have amended Claims 31, 65, and 134 to replace "thio" with the formula –SH. Support for this amendment can be found on page 20, line 27 to page 21, line 10 which permits substituents on R_C to be $-(CH_2)_pSH$, wherein p may be zero so that the formula reduces to –SH.

Applicants have amended Claim 35, 69 and 138 to delete $-(CH_2)_nNH_2$, $-(CH_2)_nNR_GH$, and $-(CH_2)_nNR_LR_M$ as possible amino groups.

Applicants have amended Claims 88, 107 and 108 to replace the term "whereby" with the term "wherein."

Applicants have amended Claim 116 such that it depends for Claim 108 alone.

Applicants have amended Claims 139 and 141-143 such that they depend from Claim 133 instead of Claim 138.

Applicants have amended Claims 176, 180, and 181 to indicate that the bone related disorders being treated are those related to bone metabolism and that the compound administered inhibits the activity of osteoclasts. Support for this amendment can be found on page 56, lines 5-6 and in Example 48D, page 117, line 36 to page 118, line 13 of the specification which indicates that compounds of the invention inhibit the activity of osteoclasts.

Applicants have amended Claim 182 to indicate that the dosage in the range of about 0.01 mg/kg of the subjects body weight and about 50 mg/kg of the subjects body weight may be administered per day. Support for this amendment can be found on page 50, line 35 to page 51, line 5 of the specification.

II. Objection to Claims 28-53, 60, 62-87, 91-93, 95-96 and 98-106

The Examiner objects to Claims 28-53, 60, 62-87, 91-93, 95-96 and 98-106 under 37 C.F.R. §1.75(c) because they are multiple dependent claims that depend from another multiply dependent claim.

Claims 28-30, 32, 34, 40, 46, 52, and 53, and the claims depending therefrom, were dependent on both Claims 20 and 25. Applicants have amended Claims 28-30, 32, 34, 40, 46, 52, and 53 such that they depend from Claim 20 alone. Applicants have added new Claims 196-220 to cover the subject matter of Claims 28-30, 32, 34, 40, 46, 52, and 53, and the claims depending therefrom, that were dependent on Claim 25.

Claims 60, 62-64, 66, 68, 74, 80, 86, and 87, and the claims depending therefrom, were dependent on both Claims 55 and 59. Applicants have amended Claims 60, 62-64, 66, 68, 74,

80, 86, and 87 such that they depend from Claim 55 alone. Applicants have added new Claims 221-248 to cover the subject matter of Claims 60, 62-64, 66, 68, 74, 80, 86, and 87, and the claims depending therefrom, that were dependent on Claim 59.

Claims 91-93, 95, 96, 98-100, and 103-105, and the claims depending therefrom, were dependent on both Claims 89 and 90. Applicants have amended Claims 91-93, 95, 96, 98-100, and 103-105 such that they depend from Claim 89 alone. Applicants have added new Claims 249-262 to cover the subject matter of Claims 91-93, 95, 96, 98-100, and 103-105, and the claims depending therefrom, that were dependent on Claim 90.

In the claims, as amended, there are no multiple dependent claims that depend from another multiple dependent claim. Therefore, Applicants request that the objection be reconsidered and withdrawn.

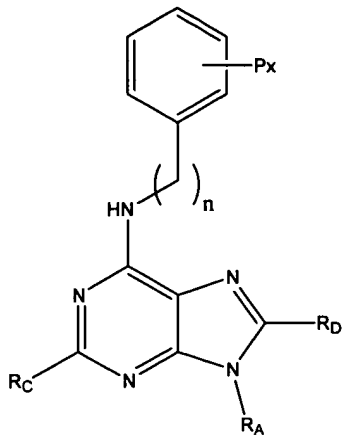
III. Rejection of Claims 1-5, 7, 12-17, 107, 112, 114, 116, 122-124, 175-178, 180, 182-183 Under 35 U.S.C. § 102(b) Over Dang, *et al.*, U.S. Patent No. 6,284,748 (Hereinafter "Dang")

The Examiner states that species 18-26, 47-54, 192-193, and 260-266 of Dang anticipate Claims 1-5, 7, 12-17, 107, 112, 114, 116, 122-124, 175-178, 180, 182-183 of the instant application. The Examiner also states that the bone treatment claims are included in the rejection because diabetes is well known as a cause for osteomyelitis.

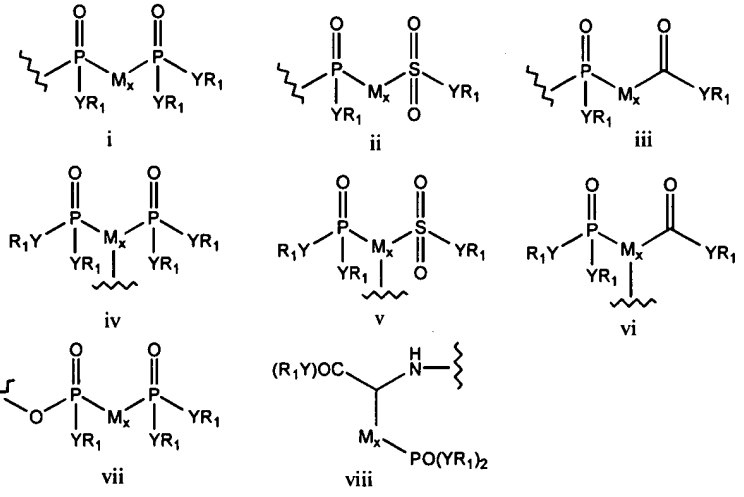
Compounds 18-26, 47-54, 192-193, and 260-266 of Dang all have a furanyl substituent at the C8 position of an adenine base. Applicants have amended Claim 1 such that R_D is H. Therefore, as amended, Applicants Claim 1, and the claims depending therefrom, are not anticipated by Dang.

Claim 176, as amended, claims a method of treating bone-related disorders involving bone metabolism by administering a compound represented by formula I. Bone metabolism involves an appropriate balance of osteoblasts, which function to form bone tissue, and osteoclasts, which function to resorb bone tissue to maintain structural integrity and proper functioning of the skeleton (page 1, lines 23-28 of the specification). Osteomyelitis is a bone infection that does not involve bone metabolism. Therefore, since Dang does not disclose any compounds that inhibit the activity of osteoclasts, Dang does not anticipate Claim 176, or the claims depending therefrom.

Claim 180 of the instant application claims a method of treating or preventing bone disorders by administering a compound that has the following structural formula:



As can be seen from the above structure, the exocyclic amine group at C6 of the compounds utilized in the method of Claim 180 are substituted with a phenalkyl group that is further substituted with Px. Px is a phosphorus containing moiety having the formula $-P(X)YR_GYR_H$ or a phosphorus containing moiety having any one of structures i-viii:



None of the purine compounds disclosed by Dang for treating diabetes have an exocyclic amine group at C6 that is substituted with a group that has a phosphorus containing moiety. Therefore, Dang does not anticipate Claim 180, or the claims depending thereform.

IV. Rejection of Claims 1-3, 6-7, 9, 14, 16 and 111 Under 35 U.S.C. § 102(b) Over Kondo, *et al.*, *Makromol. Chem., Rapid Commun.* (1980), *1*:303-306 (Hereinafter "Kondo")

The Examiner states that compound Claims 1-3, 6-7, 9, 14, 16 and 111 are anticipated by compound 4b disclosed by Kondo.

Compound 4b disclosed by Kondo does not anticipate Applicants' Claim 1, as amended, because R_B, which is attached to the exocyclic amine in formula I of Applicants' Claim 1, must be an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety which can be optionally substituted with one or more phosphorus moiety.

In compound 4b of Kondo, the exocyclic amine group of an adenine base is not attached to an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, as required by Applicants' Claim 1, but is instead attached directly to a phosphorus containing moiety. Therefore, compound 4b of Kondo does not anticipate Applicants' Claim 1, and the claims depending therefrom, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

V. Rejection of Claims 1-5, 7, 9, 14, and 16 Under 35 U.S.C. § 102(b) Over Filipov, *et al.*, *Nucleosides & Nucleotides* (1997), *16*(7-9):1403-1406 (Hereinafter "Filipov")

The Examiner states that compound Claims 1-5, 7, 9, 14, and 16 are anticipated by compounds 5 and 6 disclosed by Filipov.

Compounds 5 and 6 disclosed by Filipov do not anticipate Applicants' Claim 1, as amended, because compounds 5 and 6 of Filipov each have a phosphorus moiety attached directly to the exocyclic amine group of an adenosine base. In formula I of Applicants' Claim 1, the exocyclic amine is attached to R_B which must be an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. Since the exocyclic amine group of compounds 5 and 6 of Filipov is not attached to an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, compounds 5 and 6 of Filipov do not anticipate Applicants' Claim 1, and the claims depending therefrom. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

VI. Rejection of Claims 1-5, 7, 9, 14, and 16 Under 35 U.S.C. § 102(b) Over Tate, *et al.*, *Nature* (1979), *280*:697-699 (Hereinafter "Tate")

The Examiner states that compound Claims 1-5, 7, 9, 14, and 16 are anticipated by compounds 1 and 9 disclosed by Tate.

Compounds 1 and 9 disclosed by Tate do not anticipate Applicants' Claim 1, as amended, because compounds 1 and 9 of Tate each have a phosphorus moiety attached directly to the exocyclic amine group of an adenosine base. In formula I of Applicants' Claim 1, the exocyclic amine is attached to R_B which must be an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. Since the exocyclic amine group of compounds 1 and 9 of Tate is not attached to an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, compounds 1 and 9 of Tate do not anticipate Applicants' Claim 1, and the claims depending therefrom. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

VII. Rejection of Claims 1-5, 7, 9, 14, and 16 Under 35 U.S.C. § 102(b) Over Wada, *et al.*, *J. Am. Chem. Soc.* (1994), *116*:9901-9911 (Hereinafter "Wada")

The Examiner states that compound Claims 1-5, 7, 9, 14, and 16 are anticipated by all the products formed in Scheme 2 of Wada.

The compounds disclosed in Scheme 2 of Wada do not anticipate Applicants' Claim 1, as amended, because the compounds in Scheme 2 of Wada each have a phosphorus moiety attached directly to the exocyclic amine group of an adenosine base. In formula I of Applicants' Claim 1, the exocyclic amine is attached to R_B which must be an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. Since the exocyclic amine group of the compounds in Scheme 2 of Wada is not attached to an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, the compounds in Scheme 2 of Wada do not anticipate Applicants' Claim 1, and the claims depending therefrom. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

VIII. Rejection of Claims 1-5, 7, 9, 14, and 16 Under 35 U.S.C. § 102(b) Over Charubala, *et al.*, *Heterocycles* (1981), 15:761-776 (Hereinafter "Charubala")

The Examiner states that compound Claims 1-5, 7, 9, 14, and 16 are anticipated by compound 6 disclosed by Charubala.

Compound 6 disclosed by Charubala does not anticipate Applicants' Claim 1, as amended, because compound 6 disclosed by Charubala has a phosphorus moiety attached directly to the exocyclic amine group of an adenosine base. In formula I of Applicants' Claim 1, the exocyclic amine is attached to R_B which must be an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. Since the exocyclic amine group of compound 6 disclosed by Charubala is not attached to an aliphatic, heterocycle, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety, compound 6 disclosed by Charubala does not anticipate Applicants' Claim 1, and the claims depending therefrom. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

IX. Rejection of Claims 1-5, 7, 9, 14,16, 18, 54, 112, 114, 117, 122-123 and 175 Under 35 U.S.C. § 102(b) Over Brush, *et al.*, U.S. Patent No. 5,986,086 (Hereinafter "Brush")

The Examiner states that compound Claims 1-5, 7, 9, 14,16, 18, 54, 112, 114, 117, 122-123 and pharmaceutical composition claim 175 are anticipated by the product formed in Fig. 1B of Brush.

The product formed in Fig. 1B of Brush does not anticipate Applicants' Claim 1, and the claims depending therefrom. In Applicants' Claim 1, the adenine core structure shown in formula I has N9 substituted with R_A which can be hydrogen, an aliphatic, a heteroaliphatic, an aryl, a heteroaryl, an alkylaryl, or an alkylheteroaryl moiety. However, Applicants' Claim 1 hqs a proviso that R_A is not an aliphatic or heteroaliphatic moiety substituted with one phosphorus containing moiety (see Claim 1). Applicants have defined the term "heteroaliphatic" as aliphatic moieties which can be branched, unbranched or cyclic and which contain one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, e.g., in place of carbon atoms (p. 13, line 34 to p. 14, line 14, 6 of the specification).

The compound disclosed in Fig. 1B of Brush has N9 of the adenine ring substituted with a heteroaliphatic moiety (i.e., tetrahydrofuranyl). The heteroaliphatic moiety has two substituents, i.e., a hydroxy and a triphosphomethyl group. Since the heteroaliphatic moiety at

N9 of the compound disclosed by Brush is substituted with only one phosphorus containing moiety, the compound disclosed by Brush is excluded from the subject matter of Applicants' Claim 1 by the proviso that R_A is not an aliphatic or heteroaliphatic moeity substituted with one phosphorus containing moiety. Therefore, Applicants' Claim 1, and the claims depending therefrom, are not anticipated by Brush, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

X. Rejection of Claims 1-5, 7, 9, 14,17, 18, 54, 112, 114, 116, 117, 122-123 and 175 Under 35 U.S.C. §§ 102(b) and (e) Over Suhadolnik, *et al.*, U.S. Patent No. 6,281,201 (Hereinafter "Suhadolnik")

The Examiner states that compound Claims 1-5, 7, 9, 14,17, 18, 54, 112, 114, 116, 117, and 122-123 and pharmaceutical composition claim 175 are anticipated by the compounds 22-25 that have the base labeled Ade^{Bn} and Ade^{Bz} disclosed in Col. 4 and two phosphorus containing groups. In addition, the Examiner states that Example 8 of Suhadolnik teaches additional diphosphates and triphosphate derivatives.

Compounds 22-25 of Suhadolnik are oligonucleotide trimers in which Base1 is an adenine base that is substituted at N9 with a tetrahydrofuranyl group. The tetrahydrofuranyl group is further substituted with two phosphorus containing moieties.

Applicants claim compounds in which an adenine core structure is substituted at N9 with R_A. R_A can be a hydrogen, an aliphatic, heteroaliphatic, aryl, heteroaryl, alkylaryl, or alkylheteroaryl moiety. However, Applicants have amended Claim 1 to exclude compounds in which R_A is an aliphatic or heteroaliphatic moiety that is substituted with two phosphorus containing moieties from the claimed subject matter. Therefore, as amended, the compounds of Claim 1, and the claims depending therefrom, are not anticipated by Suhadolnik, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

XI. Rejection of Claim 10 Under 35 U.S.C. § 103(a) Over Dang

The Examiner states the stipulation of Claim 10 that C2 of Applicants' formula I is substituted with an amino group is obvious since Dang teaches that the C2 position can be substituted with an amino substituent in compounds 168-171.

As discussed above, Applicants have amended Claim 1 such that R_D cannot be a heteroaryl group. Applicants' Claim 10, which depends from Claim 1, differs from compounds 168-171 of Dang in that the C8 position is unsubstituted instead of being substituted with a furanyl ring. Since Dang does not teach or suggest any adenine compounds in which C8 is unsubstituted, Applicants' Claim 10 is non-obvious over Dang.

XII. Rejection of Claims 1-27, 54-59, 61, 88-90, 94, 97, and 107-195 Under 35 U.S.C. § 112, Second Paragraph

1. "Aliphatic"

The Examiner states that the term "aliphatic" means lacking in rings. Therefore, the Examiner believes that the term "aliphatic" is rendered indefinite by Applicants' specification which states that "aliphatic" groups can include cyclic hydrocarbons.

The Examiner's definition of the term "aliphatic" is incorrect. An aliphatic compound is a compound that is derived from methane. Thus, the essential feature of "aliphatic" compounds is that they contain only carbon and hydrogen atoms. The definition of "aliphatic" does not exclude cyclic structures. For example, the definition of the term "aliphatic" in the Van Nostrand's Scientific Encyclopedia is as follows:

> An organic compound that can be regarded as a derivative of methane, CH_4. Most aliphatic compounds are open carbon chains, straight or branched, saturated or unsaturated. See Exhibit A, *Van Nostrand's Scientific Encyclopedia*, Eighth Edition (1995), p. 95.

The statutory requirement of 35 U.S.C. § 112, second paragraph is that Applicants' use of a term would be clear to one of ordinary skill in the art. Accordingly, Applicants have clearly stated on page 11, lines 5-7 of the specification that the term "aliphatic" means that the group is a hydrocarbon (i.e., contains only carbons and hydrogen). Applicants have further indicated what types of hydrocarbons are included within the definition of the term "aliphatic" by indicating that an aliphatic group can be straight chained, branched, cyclic or polycyclic. In addition, to further clarify the scope of the claimed subject matter, Applicants have amended the claims to indicate that aliphatic groups are non-aromatic groups. Support for this amendment can be found in Applicants' examples of aliphatic groups which are all non-aromatic. Thus, when read in light

of the specification, Applicants' claims that include the term "non-aromatic aliphatic" particularly point out and distinctly claim the subject matter that Applicants regard as their invention.

2. "Aliphatic" vs. "Heteroaliphatic"

The Examiner states that the phrase "aliphatic, heteroaliphatic" is redundant because the Examiner believes that the term "aliphatic" completely encompasses the term "heteroaliphatic."

It is not relevant whether the term "aliphatic" encompasses the term "heteroaliphatic." M.P.E.P. §2173.05(h) states the following:

> The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl" should be acceptable even though 'halogen is generic to "chloro."

Therefore, Applicants respectfully suggest that it is inappropriate to reject a claim under 35 U.S.C. § 112, second paragraph because one term in a Markush group encompasses another term in the group.

Moreover, according to the definitions of the terms provided in Applicants' specification, the term "heteroaliphatic" is not encompassed by the term "aliphatic." Applicants state that an aliphatic group must be a hydrocarbon (i.e., must contain only carbons and hydrogen atoms) and give numerous examples of aliphatic groups that contain only carbon and hydrogen atoms (page 11, lines 5-24 of the specification). Applicants define the term "heteroaliphatic" as an aliphatic moiety in which one or more of the carbon atoms have been replaced with a an oxygen, sulfur, nitrogen, phosphorus or silicon atom. Thus, the term "heteroaliphatic" is not encompassed by the term "aliphatic" because heteroaliphatic groups contain heteroatoms.

3. "Substituted and Unsubstituted Aliphatic"

The Examiner states that the phrase "substituted and unsubstituted aliphatic" makes no sense because aliphatic already permits substitution.

M.P.E.P. § 2173.05(o) states that there is no per se rule against double inclusion of a claim element. The correct analysis is ". . . whether or not the multiple inclusion of one or more elements in a claim gives rise to indefiniteness in that claim." In the instant case, Applicants have stated in the specification that the terms "aliphatic," "heteroaliphatic," "alkylaryl," and "alkylheteroaryl" include substituted aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups. Applicants have also included a phrase in Claims 1, 125, 158, 176, 180, 181, 184, 186, 190, and 192 indicating that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups may be substituted or unsubstituted. Indicating in the specification that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups can be substituted or unsubstituted provides support for this provision in the claims. There is no reason to believe that a person of ordinary skill in the art would have any difficulty in determining the scope of the claims. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

4. "Heteroaliphatic"

The Examiner states that the meaning of the term "heteroaliphatic" is unclear, but appears to mean any moiety which has an atom other that a carbon or hydrogen.

Applicants define the term "heteroaliphatic" on page 13, line 34 to page 14, line 6 of the specification as follows:

> The term "heteroaliphatic," as used herein, refers to aliphatic moieties which contain one or more oxygen, sulfur, nitrogen, phosphorus or silicon atoms, e.g., in place of carbon atoms. Heteroaliphatic moieties may be branched, unbranched or cyclic and include saturated and unsaturated heterocycles such as morpholino, pyrrolidinyl, etc.

As can be seen from Applicants' definition, a heteroaliphatic group does not permit any atom to replace a carbon or hydrogen of an aliphatic group but limits the substitution to an oxygen, sulfur, nitrogen, phosphorus or silicon atoms. Applicants have further indicated that the term

"heteroaliphatic" includes straight chained, branched, or cyclic moieties, and includes saturated and unsaturated hetercycles. In addition, to further clarify the scope of the claimed subject matter, Applicants have amended the claims to indicate that heteroaliphatic groups are non-aromatic groups. Support for this amendment can be found in Applicants' examples of heteroaliphatic groups which are all non-aromatic. Thus, when read in light of the specification, a person of ordinary skill in the art would have no difficulty determining the scope of the claims. Therefore, Applicants' respectfully request that the rejection be reconsidered and withdrawn.

5. Claim 1, Page 123, Lines 18-23

The Examiner states that because the following phrase repeats what is stated in the specification, the purpose of the phrase in Claim 1 is unclear:

> wherein in each of the foregoing groups each aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic and substituted or unsubstituted, and each aryl and heteroaryl moiety may be substituted or unsubstituted;

As discussed above, M.P.E.P. § 2173.05(o) states that there is no per se rule against double inclusion of a claim element. The correct analysis is ". . . whether or not the multiple inclusion of one or more elements in a claim gives rise to indefiniteness in that claim." In the instant case, Applicants have stated in the specification that the terms "aliphatic," "heteroaliphatic," "alkylaryl," or "alkylheteroaryl" include substituted aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups and that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic. Applicants have also included a phrase in Claim 1 indicating that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups may be substituted or unsubstituted. Indicating in the specification that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl groups can be substituted or unsubstituted and that aliphatic, heteroaliphatic, alkylaryl, or alkylheteroaryl moiety may be branched or unbranched, cyclic or acyclic provides support for these provisions in the claims. There is no reason to believe that a person of ordinary skill in the art would have any difficulty in determining the scope of the claims. Therefore, Applicants respectfully request that the rejection be reconsidered and withdrawn.

6. "Terminal functionality representing a cyano"

The Examiner states that the meaning of the above phrase, which appears in Claim 1, is unclear. Applicants have amended Claim 1 to delete the phrase, thus obviating the rejection.

7. The definition of "X"

The Examiner states that it is impossible for X to be an alkyl in Claim 3 because the phosphorus atom would then have 4 bonds and no charge. The Examiner suggests that this should be removed from the specification also.

Applicants have amended the Claims and the specification so that X in the group $-P(X)YR_GYR_H$ can be absent, =O or =S instead of an alkyl group, =O or =S. Thus, in the claims, as amended, the phosphorus atom can be either trivalent or pentavalent. As discussed above, support for this amendment can be seen in the structural formulas of compounds of the invention shown on page 106 of the specification. The structural formulas show phosphorus containing groups having the formulas $-P(O)YR_GYR_H$, $-P(S)YR_GYR_H$, and $-PYR_GYR_H$.

8. "Pharmaceutically Acceptable Derivatives"

The Examiner states that the scope of the phrase "pharmaceutically acceptable derivatives" in Claim 2 is unknown. The Examiner questions whether P can be removed.

Applicants' Claim 2 indicates that only R_1 can be a "pharmaceutically acceptable derivative" and does not suggest that the phosphorus group can be removed. Applicants defined the phrase "pharmaceutically acceptable derivatives" on page 8, line 36 to page 9, line 17 of the specification. The phrase includes pharmaceutically acceptable salts, esters or salts of esters. In addition, the phrase includes any adduct or derivative that is capable of providing a compound of the invention or metabolite or residue thereof when administered to a patient, such as a prodrug.

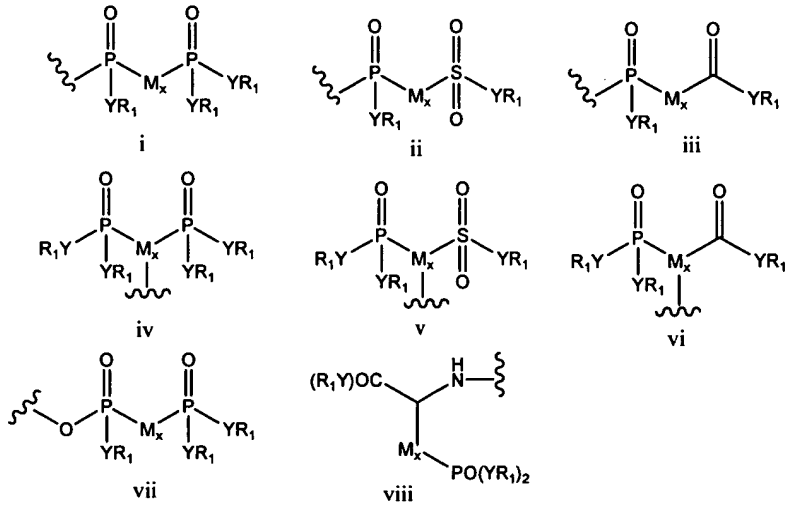
The term "pharmaceutically acceptable salts" is well known in the art (see S. M. Berge, et al., *J. Pharmaceutical Science*, *66*:1-19 (1977) for a detailed description of pharmaceutically acceptable salts) and is defined by Applicants on page 36, lines 5-33 of the specification. Pharmaceutically acceptable salts are those that within the judgement of the medical community provide a reasonable benefit/risk ratio to a patient. Applicants have given numerous examples of salts that have been deemed pharmaceutically acceptable. The term "pharmaceutically acceptable ester" is defined on page 36, line 34 to page 37, line 9 of the specification as esters

that hydrolyze *in vivo* to leave the parent compound or a salt thereof. A person of ordinary skill in the art would readily be able to determine which esters would be hydrolyzed *in vivo*. The term "pharmaceutically acceptable prodrugs" is well known in the art (see T. Higuchi and V. Stella, Pro-drugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, for a detailed description of pharmaceutically acceptable prodrugs) and is defined on page 37, lines 10-22 of the specification as prodrugs of the compounds of the invention that within the judgement of the medically community provide a reasonable benefit/risk ratio to a patient. In addition, Applicants have provided examples of pharmaceutically acceptable prodrugs on page 121, line 20 to page 122, line 12 of the specification. Thus, with the guidance provided in Applicants' specification and knowledge that is readily available, a person of ordinary skill in the art would be able to determine the scope of the term "pharmaceutically derivatives."

9. Anticedent basis for "Pharmaceutically Acceptable Derivatives"

The Examiner states that there is no provision for "pharmaceutically acceptable derivatives" in Claim 1 so that the term in Claim 2 is improper.

Claim 1 states that "at least one of R_A, R_B, R_C or R_D is substituted by one or more phosphorus moieties." Claim 2 states that one or more phosphorus containing moiety can be any one of structures i-viii:



Claim 2 states that R_1 in structural formulas i-viii can be a pharmaceutically acceptable derivative. Therefore, there is anticedent basis for the term "pharmaceutically acceptable derivative" in Claim 2 since the term "phosphorus containing moiety" appears in Claim 1 and Claim 2 claims various types of phosphorus containing moieties, some of which may have a substituent that is a pharmaceutically acceptable derivative.

10. "Comprising"

The Examiner states that the term "comprising" in the preamble of Claim 1 should be deleted. Applicants have amended the claim to delete the term.

11. "Alkylaryl"

The Examiner states that the term "alkylaryl" in Claim 1 appears superfluous since aryl is already permitted to have any kind of substituent.

The term "alkylaryl" refers to an aryl group that is attached to a compound via an alkyl group. Although Applicants' specification allows an aliphatic group to be substituted with an aryl group to arrive at a similar moiety, this does not render the scope of the claim unclear. Therefore, Applicants respectfully suggest that it is inappropriate to reject a claim under 35 U.S.C. § 112, second paragraph because one term in a Markush group encompasses another term in the group.

12. "Alkylheteroaryl"

The Examiner states that the term "alkylheteroaryl" in Claim 1 appears superfluous since aryl is already permitted to have any kind of substituent.

The term "alkylheteroaryl" refers to a heteroaryl group that is attached to a compound via an alkyl group. Although Applicants' specification allows an aliphatic group to be substituted with a heteroaryl group to arrive at a similar moiety, this does not render the scope of the claim unclear. Therefore, Applicants respectfully suggest that it is inappropriate to reject a claim under 35 U.S.C. § 112, second paragraph because one term in a Markush group encompasses another term in the group.

13. Bonds to "M"

The Examiner states that the 3rd, 4th, and 5th structures in Claim 2, on page 124, line 15 are in error because the bond to M would mean that the O or S would have threee bonds, the N would have four bonds, or the C would have five bonds.

Applicants believe that the Examiner is referring to structures iv, v and vi which show three bonds around M instead of structures iii, iv and v. Applicants have amended Claims 55, 125, 158, 180, 181, 186, and 196 and the specification such that M is CH, CH_2, CV, CHV, COH, CHOH, or CV_2, wherein in structures i, ii, iii, vii, and viii M is not CH, CV or COH and in structure iv, v, and vi one M is CH, CV or COH. In addition, Applicants have amended Claims 2, 20, 89, 108, 177, 185, and 191 and the specification such that M is CV, CV_2, -NV-, N, -O- or -S-, wherein in structures i, ii, iii, vii, and viii M is not CV or N and in structure iv, v, and vi one M is CV or N. These amendments correct the error in the valency of M in the claims and the specification. A person of ordinary skill in the art would immediately realize the obvious error in the valency and be able to discern the structure inserted herein by amendment. Therefore, the amendment does not constitute new matter.

14. Definition of "Y"

The Examiner states that the last choice for Y (i.e., $N(R_J)_2$) is an error because there would be four bonds around N but there is no charge on N.

Applicants have amended Claims 2, 3, 8, 20, 21, 25, 55, 59, 89, 90, 94, 108, 112, 125, 158, 177, 179, 180, 181, 185, 186, 191, and 192 to replace $-N(R_J)_2$ with $-NR_J-$ as a choice of substituent for Y. As discussed above, support for this amendment can be found in the definition of the term "phosphorus containing moiety" on page 15, lines 19-21 of the specification which indicates that a phosphorus containing moiety can be a phosphonic acid amide.

15. Claim 7

The Examiner states that the phrase "R_A, R_B, or R_C is additionally substituted with 0-3 substituents" in Claim 7 makes no sense because if the number is zero there is no additional substitution.

At least one of R_A, R_B, or R_C is substituted with a phosphorus containing moiety according to Claim 1 or Claim 2. In Claim 7, Applicants are claiming the embodiments wherein

R_A, R_B, or R_C have no additional substituent or have from one to three additional substituents. A person of ordinary skill in the art would have no difficulty in understanding that zero additional substituents means that R_A, R_B, or R_C have no additional substitution. Therefore, the scope of the claim is clear.

16. "Amido"

The Examiner states that the term "amido" is indefinite because there is no way of knowing whether carboxylic acid amides, sulfonic amides or phosphonic amids are intended, and even if carboxylic acid amides are intended, there is no way of knowing the point of attachment of the amide moiety.

Applicants have amended Claim 7, 8, 21, 26, 60, 90, 96, 114, 129, 178, and 179 to replace the term "amido" with -$CONH_2$, -CONH-alkyl, -CONH-aryl, -CONH-heteroaryl, -NHC(O)-alkyl, -NHC(O)-aryl, and -NHC(O)-heteroaryl. Support for this amendment can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

17. "Ketone" and "Aldehyde"

The Examiner states that the choices "ketone" and "aldehyde" as substituents are impossible because they are molecules and have no valence with which to attach.

Applicants have amended Claim 7, 8, 21, 26, 60, 90, 96, 114, 129, 178, and 179 to replace the term "ketone" with -C(O)-alkyl, -C(O)-aryl, -C(O)-heteroaryl. In addition, Applicants have replaced the term "aldehyde" with the chemical structure of an aldehyde (i.e., -C(O)H). The chemical structures show the point of attachment of the substituents. Support for these amendments can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

18. Claim 182

The Examiner states that the scope of Claim 182 is unclear because it is unclear how often the dosage range given in the claim is to be given.

Applicants have amended Claim 182 to indicate that the dosage range is to be administered once daily. Support for this amendment can be found on page 50, line 35 to page 51, line 5 of the specification.

19. "Acyl"

The Examiner states that the term "acyl" (e.g., in Claim 7 at page 125, line 21 of the specification) is indefinite because it is unclear whether acids of S, P, or As are included or if acyl is –C(O)R, what R is.

The term "acyl" appears in Claims 7, 8, 21, 26, 60, 90, 96, 114, 129, 178, and 179 as part of the term "acylamino." Applicants have deleted the term "acylamino" from Claims 7, 8, 21, 26, 60, 90, 96, 114, 129, 178, and 179.

The term "acyl" also appears in Claims 31-33, 65-67 and 134-136 as part of the term "acyloxy". Applicants have replaced the term "acyloxy" in the claims with -C(O)-alkyl, -C(O)-aryl, and -C(O)-heteroaryl. Support for this amendment can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

20. "Sulfonyl"

The Examiner states that the term "sulfonyl" in Claim 7, page 125, line 22 and in Claim 8, page 26, line 19 does not make sense because the term "sulfonyl" means the divalent radical, $-SO_2-$.

Applicants have amended Claims 7, 8, 21, 26, 60, 90, 96, 114, 129, 178, and 179 to replace the term "sulfonyl" with $-SO_2$-alkyl and $-SO_2$-aryl. Support for this amendment can be found on page 11, line 35 to page 12, line 11, page 12, line 34 to page 13, line 10 and page 13, line 34 to page 14, line 12 of the specification.

21. "Sulfate"

The Examiner states that the term "sulfate" in the claims makes no sense because the Examiner believes that sulfate is a trivalent moiety.

Applicants have submitted herewith Exhibit B which shows examples of carbohydrates substituted with sulfate groups from the IUPAC website (see section 24.3). As can be seen from

Exhibit G, the term "sulfate" refers to the anionic group $-OSO_3^-$. Since a sulfate group is monovalent, not trivalent, Applicants respectfully request that the rejection be reconsidered and withdrawn.

22. "Phosphorus Containing Moeity"

The Examiner states that the intended scope of the phrase "phosphorus containing moiety" is unclear because the discussion of the phrase in the specification is open ended. The Examiner specifically asks whether the phrase is intended to include cationic substituents that have a phosphate anion as a counter ion, whether phosphorus atoms without functional groups, such as $-PO_2$ or phosphazene rings, are included, and whether highly reactive phosphorus moieties, such as $-PCl_2$, are included.

The phrase used, for example, in Claim 1, "R_A, R_B, or R_C is substituted by one or more phosphorus containing moiety" is completely clear without additional definition. It is any moiety that can be a substituent of R_A, R_B, or R_C that contains a phosphorus atom. Applicants have listed numerous examples of phosphorus containing moieties in the specification on page 15, line 19 to page 18, line 15 as guidance to a person of ordinary skill in the art. In determining that the claim language fulfilled the requirements of 35 U.S.C. § 112, second paragraph, the Court of Customs and Patent Appeals stated in *In re Miller* the following:

> If those skilled in the art can tell whether any particular PTFE powder is or is not within the scope of a claim, the claim fulfills its purpose as a definition. *In re Miller*, 169 U.S.C.Q. 597, 599 (C.C.P.A 1971).

Likewise, in the instant case, since a person of ordinary skill in the art could readily determine whether a substituent contains a phosphorus atom, the subject matter encompassed by the term is not indefinite. Therefore, rejection of the claims under 35 U.S.C. § 112, second paragraph is inappropriate.

23. Claim 140

The Examiner states that Claim 140 is improperly dependent on Claim 139 because the last two choices in Claim 140 are cycloalkyl groups not alkyl groups.

Claim 139 states that R_C is an amino group substituted with an alkyl moiety and Claim 140 limits the alkyl moiety to methyl, ethyl, propyl, butyl, pentyl, hexyl, cyclopentyl, or cyclohexyl. Page 11, lines 10-11 of Applicants' specification defines the term "alkyl" to include ". . . both straight, branched and cyclic alkyl groups" Thus, the term "alkyl" in Claim 139 provides proper antecedent basis for the cyclopentyl and cyclohexyl groups in Claim 140.

24. "Prodrug Thereof"

The Examiner states that the phrase "prodrug thereof" in Claims 2, 20, etc. is indefinite because determining whether a given derivative is or is not a prodrug would involve more than routine experimentation.

Applicants have defined the term "prodrug" as compounds that are rapidly transformed *in vivo* to yield a compound of the invention (page 37, lines 16-18 of the specification). There are many methods known to those skilled in the art for determining whether a compound is rapidly transformed *in vivo* and for determining the products of the transformation. For example, one or more atoms of the compound could be isotopically labeled. Thus, determining whether a compound is a prodrug would only require routine experimentation that would not constitute undue experimentation.

Furthermore, since the rejection is under 35 U.S.C. § 112, second paragraph, it is not relevant whether undue experimentation would be necessary to determine whether a compound is a prodrug. It is only relevant whether a person of ordinary skill in the art would be able to determine the scope of the claimed subject matter. Since a person of ordinary skill in the art could determine the active metabolite of a prodrug using techniques known to those skilled in the art, the phrase "prodrug thereof" is not indefinite.

25. "Scaffold"

The Examiner asks what the role of the term "scaffold" is in Claim 1.

Applicants have deleted the proviso in which the term "scaffold" appears thus obviating the rejection.

26. "Protected Forms"

The Examiner states that the compounds of Claim 8 are final products so he does not understand what there is to protect against. The Examiner also states that correct selection of a protecting group requires some knowledge of what is being protected against.

Applicants wish to clarify that although the compounds in Claim 8 may be final products, they do not have to be final products. Protecting groups for a particular functional group are well known in the art. Since Applicants do not limit the compounds claimed to compounds that are stable under particular reaction conditions, it is irrelevant what each individual protecting group is protecting against. Applicants claim any protecting group for the functional groups listed in the claim.

M.P.E.P. § 2173.04 makes clear that the issue involved in a rejection under 35 U.S.C. § 112, second paragraph is not the breadth of a claim but whether the scope of the subject matter claimed would be clear to a person of ordinary skill in the art. A person of ordinary skill in the art would have no difficulty determining whether a group is a protecting group for a particular functionality. For example, "Protective Groups in Organic Synthesis," 3rd Edition, by Greene, et al., which is incorporated by reference in Applicants' specification on page 10, lines 10-13, lists many protecting groups for each functional group. Since protecting groups for a particular functionality can be readily identified by those skilled in the art, the scope of the claimed subject matter is clear, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

27. Claim 8, Page 127, Line 7

The Examiner states that the last choice on page 127, line 7 is superfluous because it is already covered by the previous term.

As discussed above, it is not relevant whether the term "-$(CH_2)_pNR$-lower alkyl" encompasses the preceeding term, "-$(CH_2)_pN(R)_2$." M.P.E.P. §2173.05(h) states the following:

> The mere fact that a compound may be embraced by more than one member of a Markush group recited in the claim does not necessarily render the scope of the claim unclear. For example, the Markush group, "selected from the group consisting of amino, halogen, nitro, chloro and alkyl"

should be acceptable even though 'halogen is generic to "chloro."

Therefore, Applicants respectfully suggest that it is inappropriate to reject a claim 35 U.S.C. § 112, second paragraph because one term in a Markush group encompasses another term in the group.

28. Claim 8, Page 26, Lines 17 and 18

The Examiner states that the terms "lower alkyl" and "lower alkenyl" are superfluous because they are covered by the terms "–$(CH_2)_p$alkyl" and "–$(CH_2)_p$alkenyl," respectively.

As discussed in the previous section, it is not relevant whether the term "lower alkyl" is encompassed by the term "–$(CH_2)_p$alkyl" or whether the term "lower alkenyl" is encompassed by the term "-$(CH_2)_p$alkenyl." If the claimed subject matter is clear, the claim meets the requirements of 35 U.S.C. § 112, second paragraph.

29. Claim 122

The Examiner states that the last line of Claim 122 is of unknown purpose. The Examiner believes that since –OH is already a permitted substituent if the phrase "optionally substituted by one or more hydroxyl moieties" were removed the scope of the claim would be the same.

Applicants disagree with the Examiner's interpretation of the claim. The phrase "optionally substituted by one or more hydroxyl moieties" limits R_A to an aliphatic group which is unsubstituted or to an aliphatic group which is substituted with one or more hydroxyl group. This limitation does not appear in any of the claims from which Claim 122 depends. Therefore, the the phrase is not superfluous.

30. "Thio"

The Examiner states that the term "thio" is generic indicating the presence of sulfur in some form.

The term "thio" appears in Claims 31, 65, and 134 and is a choice of substituent on R_C. Applicants have amended these claims to replace "thio" with the formula –SH. Support for this

amendment can be found on page 20, line 27 to page 21, line 10 which permits substituents on R_C to be $-(CH_2)_pSH$, wherein p may be zero so that the formula reduces to –SH.

31. Dependancy of Claim 138

The Examiner states that Claim 138 is improperly dependent on Claim 137 when n is not equal to zero.

Applicants have amended Claim 138 to delete $-(CH_2)_nNH_2$, $-(CH_2)_nNR_GH$, and $-(CH_2)_nNR_LR_M$. Applicants have made a similar amendment to Claims 35 and 69.

32. Dependancy of Claims 139-143

The Examiner states that Claims 139-143 are improperly dependent on Claim 138.

Applicants have amended Claims 139 and 141-143 such that they depend from Claim 133.

33. Variable "HA"

The Examiner states that the variable "HA" is not defined in Claim 158.

The variable "HA" is defined in Claim 158 at the end of the first paragraph under the structural formula.

34. "Bone-Related Disorder"

The Examiner ask what the term "bone-related disorder" is and how does it differ from the term "bone disorder" that appears in Claim 180.

Applicants have amended Claims 176, 180 and 181 to delete the terms "bone-related disorder" and "bone disorder." Applicants have amended these claims to indicate that the disorders being treated involve bone metabolism. Applicants' specification indicates that term "bone metabolism" refers to the balance between formation of bone tissue by osteoblasts and resorption of bone tissue by osteoclast (page 1, lines 23-28 of the specification). Thus, Claims 176, 180, 181, and the claims depending therefrom, are directed to a subset of bone disorders that are related to the activity of osteoblasts and osteoclasts.

35. Claim 18

The Examiner states that the phrase "one of more" in line 2 of Claim 18 is unclear.

Applicants have amended Claim 18 such that the phrase reads "one or more." Applicants have corrected a similar typographical error in Claims 53, 87, 104, 122, 157, and 172.

36. Claim 88

The Examiner states that the first "whereby" clause is not clear because if R_C is an aryl, for example, the condition cannot be met.

Applicants have amended Claim 88 to replace the term "whereby" with the term "wherein."

37. Claim 107

The Examiner states that the same problem that existed with the "whereby" clause in Claim 88 is also present in Claim 107.

Applicants have amended Claim 107 to replace the term "whereby" with the term "wherein."

38. Dependancy of Claim 116

The Examiner states that Claim 116 cannot depend from Claim 112 because R_1 does not exist in Claim 112.

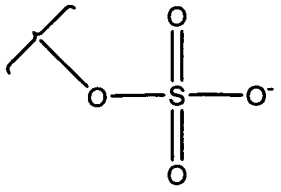
Applicants have amended Claim 116 such that it depends from Claim 108 only.

XIII. Rejection of Claims 7-18, 21, 26, 90, 114, 129, 178, and 179 Under 35 U.S.C. § 112, First Paragraph

A. "Sulfate"

The Examiner states that if sulfate is a monovalent substituent it will have a net negative charge. The Examiner believes this is impossible if no cation is provide for in the claim.

Applicants would like to clarify that a sulfate substituent has a net charge of -1 and can be represented by the following structural formula:

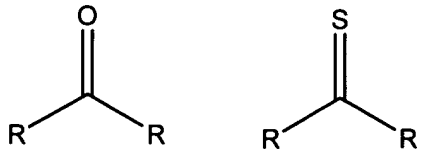


Applicants disagree that it is impossible to have an anionic compound that does not have an associated cation. For example, when an anionic compound is in solution it dissociates from its cation so that the cation can no longer be considered part of the compound. Since it is not impossible to have an anionic compound that does not have an associated cation, Applicants respectfully request that the rejection be reconsidered and withdrawn.

B. "Carbonyl" and "Thiocarbonyl"

The Examiner states that a carbonyl has the structural formula =C=O and a thiocarbonyl has the structural formula =C=S and that these functional groups are too reactive for pharmaceuticals.

Applicants disagree with the structural formulas that the Examiner gives for a carbonyl group and a thiocarbonyl. A carbonyl and a thiocarbonyl can be represented by the following structural formulas (see Exhibit C):



carbonyl thiocarbonyl

Thus, a carbonyl group and a thiocarbonyl group would not be too reactive for a pharmaceutical compound.

Applicants have, however, amended Claims 8, 21, 26, 90, 129, and 179 to delete carbonyl and thiocarbonyl from the list of optional substituents for aromatic rings since this would result in a pentavalent carbon.

XIV. Rejection of Claims 176-183 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejects Claims 176-183 under 35 U.S.C. § 112, first paragraph because the Examiner believes that Applicants' genus of compounds covers trillions of compounds and that the scope of the term "bone disorders" is immense. In assessing the state of the art and the skill of those in the art, the Examiner states that bone disorders arise from a huge assortment of unrelated causes and that the cause of some of the disorder, such as Paget's disease, is unknown. In addition, the Examiner states that the level of skill in the art is high for some bone disorders, such as osteoporosis, but he believes that it is low for others, such as osteosarcomas for which no chemotherapy has been demonstrated. In addition, the Examiner believes that Applicants have provided no data for any specific examples and that Applicants provide only limited guidance because only a few disorders are mentioned specifically and the dosage range information given in the specification is not associated with any particular disease. Therefore, the Examiner surmises that the level of experimentation needed to practice the claimed invention would be high in view of the diversity of disorders and the breadth of the compound genus.

Claims 176, 180, and 181, and the claims depending therefrom, are directed to a method of treating bone related disorders by administering to a subject in need thereof a compound of the invention. Applicants have amended the claims such that they include only methods of treating disorders that involve bone metabolism. Applicants' specification indicates that term "bone metabolism" refers to the balance between formation of bone tissue by osteoblasts and resorption of bone by osteoclast (page 1, lines 23-28 of the specification). Thus, Claims 176, 180, 181, and the claims depending therefrom, are directed to a subset of bone disorders that are related to the activity of osteoblasts and osteoclasts.

For some diseases involving bone metabolism, the underlying cause and risk factors for the disease are well known. For example, the most common cause of osteoporosis is a reduction in estrogen production that occurs at menopause in woman. Reduction in estrogen causes the bones to lose calcium. Risk factors for the disease include being a post menopausal woman, smoking, consumption of large amounts of alcohol, having a low body weight, having a diet low in calcium, lack of exercise, a family history of osteoporosis, a medical history of overactive thyroid, liver disease or anorexia nervosa, long-term treatment with steroids, and previous fractures from minor trauma (see Exhibit D). Moreover, although the exact cause of many diseases involving bone metabolism may be unknown, they are known to involve an inbalance

between osteoblast activity (e.g., bone formation) and osteoclast activity (e.g., bone resorption). Thus, it is recognized in the art that they can be treated with compounds that modulate the activity of osteoblasts or osteoclasts. For example, Paget's disease responds positively to treatment with bisphosphonate drugs which reduce bone loss by inhibiting the activity of osteoclasts (see Exhibit E). Bisphosphonates can also be used to ameliorate the symptoms of bone cancer, such as bone discomfort or bone fracture by inhibiting osteoclast activity (see Exhibit F). Thus, although the cause of many diseases involving bone metabolism may not be known, it is generally known in the art that an effective way of treating such diseases is by inhibiting the activity of osteoclast, such as in Applicants' claimed method.

Applicants have amended the claims to indicate that the compounds used to treat bone disorders are those compounds that inhibit the activity of osteoclasts. Applicants have provided ample direction in how to determine which compounds inhibit osteoclast activity. For example, Applicants have provided an *in vitro* assay for determining whether a compound inhibits bone resorption by osteoclasts (Example 48A, page 108 to page 111 of the specification). In addition, Example 48D provides a murine model and a protocol for demonstrating whether a compound inhibits the activity of osteoclasts *in vivo* (page 117, line 36 to page 118, line 6 of the specification). Therefore, a person of ordinary skill in the art would simply have to follow the methods disclosed by Applicants to determine whether a compound is encompassed by the claimed genus would inhibit osteoclast activity.

Applicants have also demonstrated that compounds of the invention inhibit bone resorption by rabbit osteoclast with an IC_{50} in the range of about 1μM to about 100 μM (Example 48A, in particular page 110, lines 6-8 of the specification) and some compounds inhibited resorption with an IC_{50} of about 1 μM to about 20 μM (page 110, line 22 to page 111, line 11 of the specification). In addition, Applicants have disclosed particular substitutions on the core structure that will provide compounds that have IC_{50} values within the disclosed range (page 110, lines 8-12 and page 110, line 22 to page 111, line 11 of the specification). Thus, Applicants have provided guidance as to which compounds in the claimed genus are likely to have an IC_{50} in the disclosed range.

Since all the diseases for which a method of treatment is claimed are related to bone metabolism, the dosage range for treating each disease is expected to be similar. Applicants have provided guidance as to an effective dosage range for the compounds of the invention. For

example, Applicants disclose that an effective dose range for the compounds of the invention is between about 0.01 mg/kg and about 50 mg/kg per day, and is preferably between about 1 mg/kg and about 25 mg/kg per day (page 50, line 34 to page 51, line 6 of the specification). Furthermore, Applicants have used a murine hypercalcemia model (page 117, lines 24-26 of the specification) to demonstrate working examples of compounds of the invention that inhibited the activity of osteoclasts in Example 48D on page 117 to 118 of the specification by as much as 95% (page 118, lines 9-13 of the specification) when a dosage of 10 mg/kg was administered. When a dosage of 3 mg/kg was administered, the compounds inhibited osteoclast activity by up to 60%.

The Examiner also states that the skill level for preventing bone related diseases is low. In addition, the Examiner states that Claim 183, which depends from Claims 176, 180 and 181 and is directed to the treatment or prevention of osteoporosis by administering the compound of the invention, would be enabled if it depended from Claim 176 alone. Claim 176, as amended, is directed to methods of treating disorders involving bone metabolism, and does not claim methods of preventing disorders involving bone metabolism. Claims 180 and 181, as amended, claim both a method of treating and a method of preventing disorders involving bone metabolism.

Since many factors that lead to bone loss have been documented, it is foreseeable that certain individuals have a high risk of developing a bone disorder related to bone metablism. For example, individuals that are treated with steroids for conditions such as asthma or rheumatoid arthritis, are at risk for getting osteoporosis and are often given given bisphosphonates, a medication that inhibits the activity of osteoclasts, to prevent it (see Exhibit G, page 2, the first full paragraph). Thus, it is well known in the art that osteoporosis may be prevented in patients at high risk for the disease by prescribing drugs that inhibit osteoclast activity.

Bone metabolism is well understood in the art, and osteoclast inhibitors, such as bisphosphonates, have been shown to be an effective method of treating and preventing disorders involving bone metabolism. Applicants have provided *in vitro* and *in vivo* data that shows that the compounds of the invention are effective osteoclast inhibitors and have provided guidance as to what dosage range would be effective. Therefore, a person of ordinary skill in the art would not need to do undue experimentation to practice the method of Claims 176, 180, and 181, as

amended, and the claims depending therefrom. Thus, Applicants respectfully request that the rejection be reconsidered and withdrawn.

XV. Rejection of Claims 184-195 Under 35 U.S.C. § 112, First Paragraph

The Examiner rejects Claims 184-195 under 35 U.S.C. § 112, first paragraph because the Examiner believes that Applicants' genus of compounds covers trillions of compounds and that the treatment of cancer would cover hundreds of types of cancers. In assessing the state of the art and the skill of those in the art, the Examiner states that there is no known general treatment for cancer because cancer can arise from a wide variety of different sources. The Examiner also believes that adenines have never been used to treat cancer. The Examiner states that the level of skill in the art is high for some cancers, but he believes that it is low for many others. In addition, the Examiner believes that Applicants have provided no data for any specific examples and that Applicants provide only limited guidance because only a few disorders are mentioned specifically and the dosage range information given in the specification is not associated with any particular disease. Therefore, the Examiner surmises that the level of experimentation needed to practice the claimed invention would be high in view of the diversity of disorders and the breadth of the compound genus.

Claims 184-189 are directed to a method of inhibiting cancer in a subject by administering to the subject a compound of the invention; Claims 190 and 191 are directed to a method of inhibiting the growth of tumor cells by contacting the cells with a compound of the invention; and Claims 192-195 are directed to a method of inhibiting the growth of tumor cells in a subject by administering to the subject a compound of the invention.

Tyrosine kinases are enzymes that catalyze the transfer of adenosine triphosphate (ATP) to the hydroxyl group of a tyrosine residue of a protein. It is generally known in the art that tyrosine kinases play a role in tumor progression, such as tumor growth, survival, metastasis and angiogenesis, and that small molecules that compete with ATP binding at the catalytic site of the enzyme can inhibit the activity of the enzyme and be efficacious in treating cancer (see Exhibit H, abstract). In addition, chemical compounds that inhibit tyrosine kinases, such as CP-358,774, have been found to be useful in treating a broad spectrum of tumors (Exhibit H, page 6578, Col. 1, paragraph 2). Thus, it is accepted in the art that chemical compounds that inhibit tyrosine kinases can be efficacious against a broad range of cancers.

The compounds of the invention inhibit protein kinase activity (page 111, lines 14-15 of the specification). In particular, Applicants have shown that compounds of the invention inhibit scr kinase, a tyrosine kinase, *in vitro* with an IC_{50} in the range of between about 0.001 μM to about 0.1 μM (page 117, lines 6-8 of the specification). Furthermore, Applicants have used a murine hypercalcemia model (page 117, lines 24-26 of the specification) to demonstrate working examples of compounds of the invention inhibited the activity of Scr kinase *in vivo* in Example 48D on page 117 to 118 of the specification. In this model, parathyroid hormone (PHT), which stimulates calcium absorption in the intestines and increases calcium release from the bones, is given to mice to increase their serum calcium levels. Scr kinase is involved in aiding the attachment of osteoclast to the bone prior to bone resorption. Thus, if a compound inhibits the activity of Scr kinase, animals given PTH and the compound will have lower serum calcium levels than animals that were given PTH alone. Applicants have demonstrated that compounds of the invention decreased serum calcium levels by as much as 95% (page 118, lines 9-13 of the specification) when a dosage of 10 mg/kg of a compound of the invention was administered. When a dosage of 3 mg/kg was administered, the compounds decreased serum calcium levels by up to 60% (page 118, lines 9-13 of the specification). Thus, Applicants have demonstrated working examples of compounds of the invention that inhibit the activity of the tyrosine kinase, Scr kinase. These examples provide guidance to a person of ordinary skill in the art as to the dosage range necessary to inhibit the activity of tyrosine kinases *in vivo*.

Compounds that are useful in treating cancer are cytotoxic and have anti-proliferative activity. Applicants have disclosed that compounds of the invention have cytotoxicity in the range of between about 3.5 μM and about 45 μM and have disclosed examples of substituents on the adenine core structure that are most likely to provide compounds that have activity in the disclosed range (page 44, lines 5-13 of the specification). Assays to determine cytotoxicity and anti-proliferative activity of a compound are well known in the art. In addition, Applicants have provided ample guidance as to what assays may be used to determine whether a compound of the invention is cytotoxic and/or inhibits cell proliferation in Example 48E on page 118 to page 121 of the specification. In this example, both *in vitro* assays (page 118, line 29 to page 120, line 29 of the specification) and *in vivo* assays (page 120, line 30 to page 121, line 17 of the specification) are discussed. Thus, it would be a matter of route experimentation for a person of ordinary skill in the art to determine which compounds in Applicants' claimed genus have

cytotoxic and anti-proliferative activity. Furthermore, numerous compounds can be screened simultaneously in many of the assays.

It is well understood in the art that tyrosine kinases play a role in tumor progression and that small molecules that compete with ATP for the catalytic site of the enzyme can inhibit the activity of the enzyme and provide an efficacious treatment for a broad range of cancers. Applicants have shown that compounds of the invention have cytotoxic activity and inhibit tyrosine kinases, and in particular Scr kinase, in both *in vitro* and *in vivo* assays. In addition, Applicants have provided guidance as to which substituents on the adenine core structure are most likely to provide compounds that have cytotoxic and anti-proliferative activity. Therefore, a person of ordinary skill in the art would not need to do undue experimentation to practice the method of Claims 184-195, and Applicants respectfully request that the rejection be reconsidered and withdrawn.

XVI. Information Disclosure Statement

Applicants filed an Information Disclosure Statement (IDS) on December 6, 2001. However, the Examiner has indicated that the cited references were either not enclosed or were lost by the Patent and Trademark Office (PTO). Applicants submit herewith a replacement set of references, as the Examiner requests. In addition, Applicants submit herewith as Exhibit I a copy of the postcard which was received by the PTO on December 7, 2001 indicating that the PTO received copies of the cited art.

XVII. Provisional Rejection of Claims 1-27, 54-59, 61, 88-90, 94, 97, 107-195 Under the Doctrine of Obviousness-Type Double Patenting Over U.S. Applicantion No. 09/740393

The Examiner provisionally rejects Claims 1-27, 54-59, 61, 88-90, 94, 97, 107-195 under the doctrine of obviousness-type double patenting over Claims 1-18 and 35-39 of co-pending application 09/740393. The Examiner states that the claims of the applications are not identical but contain broadly overlapping subject matter.

Applicants will address this provisional rejection once allowable subject matter has been found in one of the applications cited.

XVIII. Abstract

The Examiner has objected to the Abstract on the grounds that it is too vague. Applicants have submitted herewith a substitute Abstract.

XIX. Petition for Extension of Time

Enclosed is a petition to extend the period for replying for three months, to and including July 10, 2003. Please charge any fees that may be associated with this matter, or credit any overpayments, to our Deposit Account No.03-1721.

Respectfully submitted,

Dated: 7/10/03

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